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(71) Applicant (*for all designated States except US*): THE SECRETARY OF STATE FOR TRADE AND INDUSTRY IN HER BRITANNIC MAJESTY'S GOVERNMENT OF THE UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND [GB/GB]; 10/18 Victoria Street, London SW1H 0ET (GB).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*) : HALLING, Peter, James [GB/GB]; 34 Montague Street, Glasgow G4 9HX (GB). MOODY, George, William [GB/GB]; 71 Naxwellton Avenue, East Kilbride, Glasgow G74 3AF (GB). HICKMAN, Alan, Douglas [GB/GB]; 98 Carnoustie Crescent, Greenhills, East Kilbride, Glasgow G75 8TE (GB).

(74) Agents: BECKHAM, Robert, William et al.; Ministry of Defence (PE), Patents 1A(4), Room 2014, Empress State Building, Lillie Road, London SW6 1TR (GB).

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(57) Abstract

A membrane bioreactor which provides close contact between microbial cells and a gas by culturing microbial cells on the outside of a membrane through which a culture medium can flow and passing the gas through a support matrix surrounding the membrane. The cells are too big to pass through the membrane and so are trapped on its surface in close contact with both gas and liquid. This enables high oxygen transport rates, a superior environment for growth and thus a saving in power consumption.

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MEMBRANE BIOREACTOR

This invention relates to a membrane bioreactor, particularly for use with aerobic microbial cells. Microbial cells are herein defined to include both plant and animal cells.

A biorector is a reactor in which a chemical conversion or product is made by using living organisms or parts thereof. The organisms are fed with nutrients and/or a gas, usually air or oxygen, and the resulting products are extracted from the reactor.

Conventionally, bioreactors use an aerated liquid system where the gas phase is broken up into small bubbles which are passed through a liquid nutrient medium containing microbial cells freely suspended in the liquid. This method of gas transfer to the cells is , however, highly inefficient, is essentially responsible for the high power demands of conventional liquid bioreactors, and can account for a major element of the costs in running these types of reactors. Moreover, for reasons of mal-distribution some cells may not receive sufficient oxygen to sustain the desired bioreaction resulting in a reduced product yield. Furthermore, the problems of gas supply have prevented the exploitation of immobilised cells for most aerobic microbial processes.

There are in existence a number of membrane bioreactors, for example, as proposed by Kornfield ėt al (Biotech Prog 2 98-104 1986), where the cells are in the liquid phase which is separated from the gas phase by a membrane so as to provide a large gas-liquid interfacial surface. Gas transfer to the cells occurs by diffusion of the gas across the membrane to the liquid phase. Unfortunately, this is not an efficient method of gas transfer and is therefore not an effective principle to apply to aerobic microbial cells which need to be in the closest possible contact with the gas supply in order that the products are efficiently produced.

There is therefore a need for a membrane bioreactor for use with aerobic microbial cells which produces an efficient transfer of oxygen to the cells.

According to the present invention a bioreactor consists of at least one permeable inner flow channel, a membrane permeable by liquid but not by cells defining an inner surface of the or each inner

flow channel, the or each inner flow channel being surrounded by a support matrix, such that in use microbial cells are cultured on the outside surface of the membrane.

The inner flow channels are preferably hollow fibres and the support matrix is of a macroporous ceramic material.

The bioreactor may be housed in a stainless steel or glass housing which allows for complete drainage of the bioreactor.

According to another aspect of the invention, a method of carrying out a bioreaction includes the steps of:

inoculating a bioreactor with microbial cells to the outside surface of a membrane permeable by liquid but not by cells, the membrane defining an inner surface of at least one inner flow channel;

passing a liquid culture medium through the or each inner flow channel;

passing a gas through a support matrix which surrounds the or each inner flow channel; and

extracting a product from the bioreactor.

The microbial cells are preferably aerobic microbial cells and when they are placed on the outside of the membrane, referred to as the gas side, theybecome immobilised in between the pores of the membrane. The gas used may be air or oxygen. The advantage of having the cells on the gas side in this way is that they are in the closest possible contact with the gas supply, and being immobilised the cells are supplied with nutrients from the liquid phase which diffuse across the membrane to the cells.

The present invention will now be described, by way of example only, with reference to the following diagrammatic drawings, in which:

Fig 1 is a side elevation in section of one emobodiment of the invention;

Fig 2 is an end elevation in section of Fig 1;

Fig 3 is an enlargement of a detail of Fig 1; and

Figs 4 and 5 are circuit diagrams of the plumbing, instrumentation and control systems used for the gas and liquid phases respectively.

As shown in Figs 1 and 2 a bioreactor 10 has an inner flow channel 11, surrounded by a support matrix 12. A microporous membrane

13 surrounds the inner surface of the inner flow channel 10 (the 'tube side'). As shown in Fig 3 aerobic microbial cells 20 are immobilised between the pores 21 of the membrane 13 on the outside of the membrane (the 'shell side').

In operation, the entire bioreactor is initially sterilised, preferably in situ with live steam. This prevents the growth of unwanted microbes (though in industrial operation it might not be necessary to sterilise medium, since this is separated from the microbial cells 20 by the microporous membrane 13 through which contaminants cannot pass). The reactor is then innoculated with cells by pumping a suspension to the shell side, and removing medium through the tube side by reverse flow at low pressure. When an appropriate number of cells has been loaded (preferably monitored by following transmembrane pressure difference), excess liquid is drained from the shell side. Start up of the reactor involves progressive and balanced pressurisation of each side of the membrane: with gas on the shell side and liquid nutrient medium on the tube side. Flow of each phase is then started and operation of the bioreactor is commenced. Since the aerobic microbial cells 20 are on the shell side of the membrane 13 they obtain a large supply of oxygen whilst nutrients are supplied to the cells 20 via diffusion of the liquid medium through the membrane 13. The arrangement ensures an efficient production of the required products which are produced as the cells grow in the pores 21 of the membrane 13. The products return to the liquid phase on the tube side where they are extracted from the bioreactor by known means.

Another embodiment of the invention is where the bioreactor consists of a plurality of inner flow channels 11 surrounded by a support matrix 12.

To ensure proper operation of the bioreactor a measurement and control system is used with the bioreactor. A dedicated micro-computer (not shown) is used to provide a direct digital control strategy so as to allow flexibility of placing and characteristics of control loops.

Figs 4 and 5 are examples of the type of measurement and control system which could be used with the bioreactor.

Fig 4 shows a system together with a piping scheme for use on the shell side of the membrane 13. Air is passed in at 72, passes through various components before passing through the shell side. As the air leaves the shell side it passes through a further set of components and is eventually output at 90 to drying analysers (not shown). The air is recycled via pump 40 as shown back to the input.

Fig 5 shows a system together with a piping scheme for use on the tube side of the membrane 13. A medium of aqueous solution is passed into the system at 82 and acid/alkali at 84. After mixing together and passing through various components the mixture is passed into the tube side. As the mixture leaves the tube side it passes through further components and is output at 92. Some of the mixture is also recycled through pump 44 back to the input as shown.

In the systems provision is made for recycle of fluids on both sides of the membrane, though in industrial use straight through flow would probably be used for each. The figures do not show connections needed for initial sterilisation, though sterilisation is preferably carried out in situ with live steam. The Sterile boundary 40 indicates which components and connections are sterilisable. Functions of the various components in Figs 4 & 5 will now be described: Valves 20-32 are used mainly for manual on-off operation during cleaning and inoculation and may be simple clips on flexible tubing. Valves 20, 27 and 32 are motorised actuators and measure moist compressed air (20,27) and aqueous solutions (32) and are preferably controlled by the computer. In Fig 4 pump 40 pumps the recycled moist air back to the input of the shell side and pump 41, which is inside the sterile boundary, pumps the microbial cell suspension to the input of the shell side. In Fig 5 pump 42 pumps the various aqueous solutions into the tube side and pump 43 pumps acid/alkali into the tube side of the bioreactor. Pump 44 has the function of pumping the recycled aqueous solution back into the input of the tube side. Pumps 40,42,43 and 44 are all preferably controlled by the computer.

Flow rate sensors, 50-56, are all inside the sterile boundary and so are preferably sterilisable liquid flow sensors. Sensors 50-53 measure the flow rate of moist air while sensors 54-56 measure the flow rate of the various aqueous solutions. All sensors provide electrical outputs for logging by the computer and for use in control loops. Heaters 60 and 62 are included in the shell side system to prevent condensation in sterile fitters. Also, both shell side and tube side have computer-controllable heat exchange devices 64,66 and in the gas stream (64) may be required to remove heat. A humidifier 70 is also included on the shell side (Fig 4) and under the control of the computer controls the input of water vapour into the compressed air stream 72. An in-line mixer 80 in Fig 5 mixes the medium input 82 and the input of acid/alkali 84 and has as small a volume as possible. Various other parameters of the gas and liquid are also measured such as temperature, pressure, humidity, pH and dissolved oxygen tension and are indicated by T, P, H, pH and DOT respectively in Figs 4 and 5.

It will be realised that other arrangements of the bioreactor and measurement and control system are possible within the scope of the invention.

CLAIMS

What is claimed is:

1. A bioreactor consisting of at least one permeable inner flow channel, a membrane permeable by liquid but not by cells defining the inner surface of the or each inner flow channel, the or each inner flow channel being surrounded by a support matrix, such that in use microbial cells are cultured on the outside surface of the membrane.

2. A bioreactor as claimed in Claim 1 wherein the or each inner flow channel is a hollow fibre.

3. A bioreactor as claimed in Claim 1 or Claim 2 wherein the support matrix is a macroporous ceramic material.

4. A bioreactor as claimed in any previous claim wherein the bioreactor is housed in a glass housing.

5. A bioreactor as claimed in Claim 1 to 3 wherein the bioreactor is housed in a stainless steel housing.

6. A bioreactor as claimed in Claim 4 or 5 wherein the housing allows for complete drainage.

7. A bioreactor as claimed in any previous claim which further includes a first measurement and control system for use with an inlet for the gas including a humidifier, heating means, a pump and sensors for measuring flow rate humidity, temperature and pressure and further includes, for use with an outlet for the gas heating means and sensors for measuring pressure, temperature, himidity and flow rate.

8. A bioreactor as claimed in any previous claim which further includes a second measurement and control system for use with an inlet for the liquid medium including a first pump, heating means, an inlet for acid or alkali, a second pump, a mixer and sensors for measuring flow rate, pH, temperature, pressure and dissolved oxygen tension of the medium and further includes, for use with an outlet for the medium, sensors for measuring pressure, temperature, dissolved oxygen tension. pH and flow rate.

9. A bioreactor as claimed in Claim 7 wherein the measurement and control system further includes feedback means to recycle the gas.

10. A bioreactor as claimed in Claim 8 wherein the measurement and control system further includes feedback means to recycle the medium.

11. A bioreactor as claimed in any one of Claims 7 to 10 wherein the measurement and control system further includes a computer.

12. A method carrying out a bioreaction including the steps of;
innoculating a bioreactor with microbial cells to the outside surface of a membrane permeable by liquid but not by cells, the membrane defining an inner surface of at least one permeable inner flow channel;
passing a liquid culture medium through the or each inner flow channel;
passing a gas through a support matrix which surrounds the or each inner flow channel;
and extracting a product from the bioreactor.

13. A method of carrying out a bioreaction as claimed in Claim 12 wherein the microbial cells are aerobic microbial cells.

14. A Method of carrying out a bioreaction as claimed in Claim 12 wherein the gas in air.

15. A method of carrying out a bioreaction as claimed in Claim 12 wherein the gas is oxygen.

16. A bioreactor substantially as herein described with reference to the accompanying drawings.

17. A method of carrying out a bioreaction substantially as herein described.

Fig. 1.

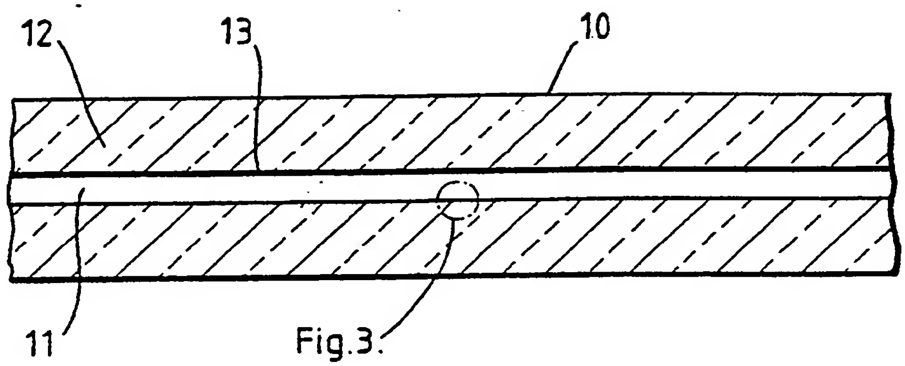
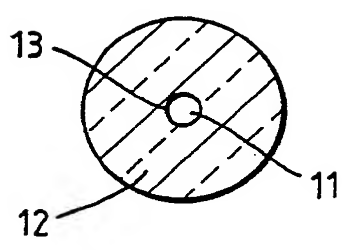


Fig. 3.

Fig. 2.



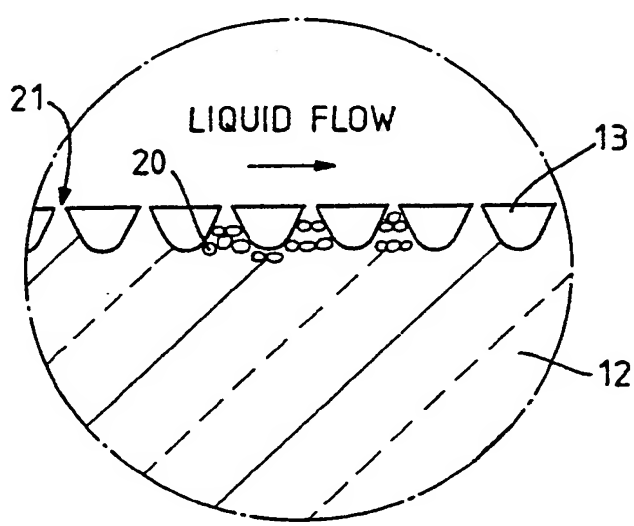


Fig.4.

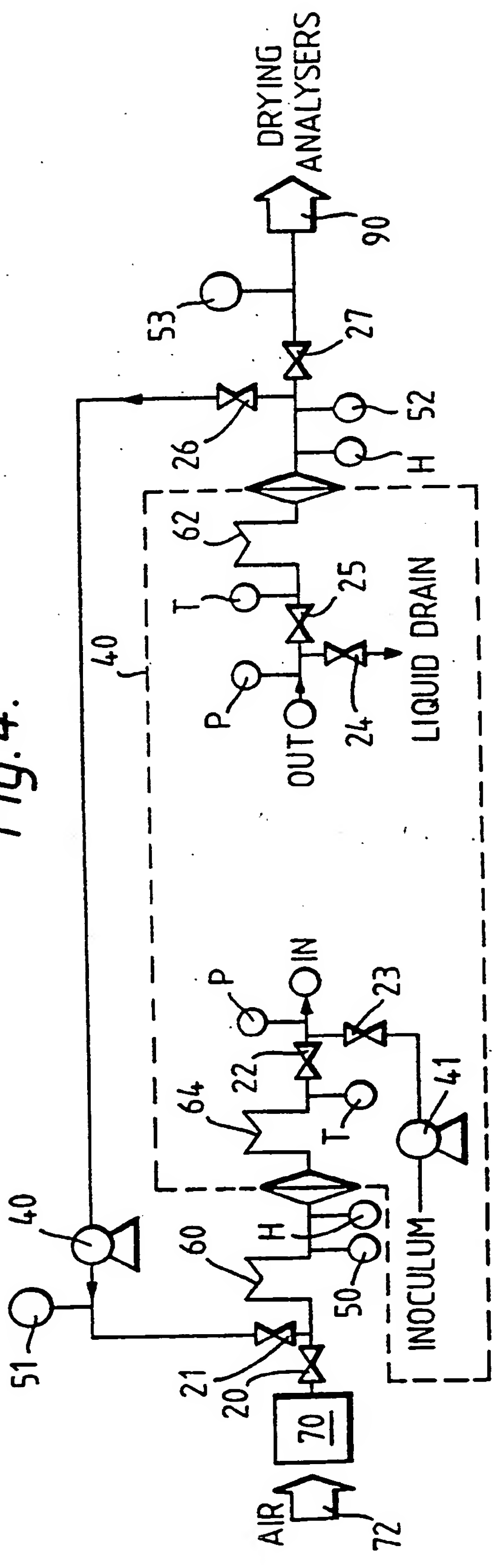

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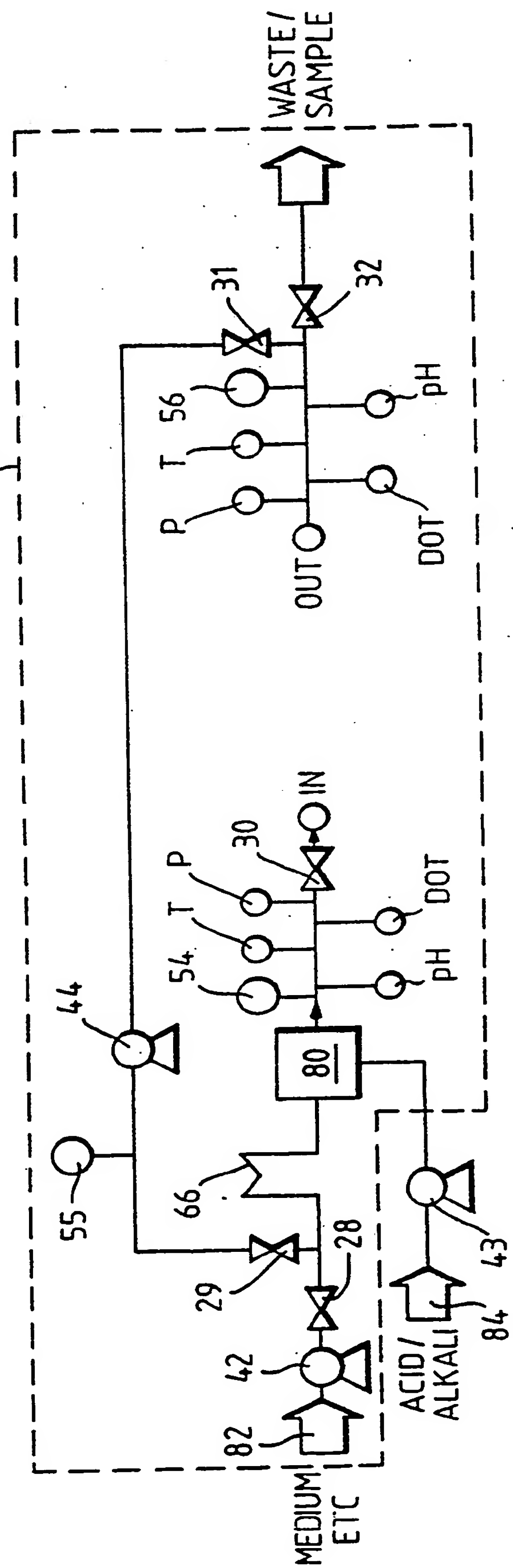
Fig.5.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